REMARKS

Claims 19-20, 22-23, 26-33 are currently pending in the present application. Claim 21 has been cancelled. The Office Action is non-final. Claims 27-30 are withdrawn from further consideration as being directed to a non-elected invention. Claims 19-23 and 26 stand rejected.

Examined claims 19-23, 26 and 31-33 considered together with the following remarks are believed sufficient to place the application into condition for allowance. Accordingly, an early and favorable action on the merits is earnestly solicited at present.

Application Data Sheet

The Examiner objects to the Application Data Sheet (ADS) on record at the PTO.

In response to this objection, Applicants are submitting a supplemental ADS with necessary corrections pursuant to 37 C.F.R. § 1.76(c).

Sequence Listing

Enclosed herewith in full compliance with 37 C.F.R. §§1.821-1.825 is a Substitute Sequence Listing to be inserted into the specification as indicated above. The Substitute Sequence Listing in no way introduces new matter into the specification. Also submitted herewith in full compliance with 37 C.F.R. §§1.821-1.825 is an electronic CRF copy of the Substitute Sequence Listing. The electronic CRF copy of the Substitute Sequence Listing, file "2008-11-20 0552-0160PUS1_ST25.txt", is identical to the paper copy, except that it lacks formatting. In no way do the paper copy nor the electronic CRF copy of the Substitute Sequence Listing introduce new matter into the application.

The specification is amended to properly identify each disclosed sequence with a corresponding sequence identification number (SEQ ID NO). The Sequence Listing is amended to update the file reference number. Furthermore, the sequences of SEQ ID NOS: 9 and 10 have been added to the enclosed Sequence Listing. The sequences of SEQ ID NOS: 9 and 10 can be

found in the specification as indicated in the above amendments. No new matter is introduced by these amendments.

Objections to the Specification

(a) The specification is objected to for disclosing a peptide sequence of ≥4 amino acids in length and fails to comply with 37 C.F.R. § 1.821 -1.825.

In response to this objection, Applicants have updated the specification to provide sequence identifiers pursuant to 37 C.F.R. § 1.821 -1.825 and submitted a substitute Sequence Listing.

(b) Figure 2 is objected to for reciting the same description for panels 2A-2D.

In response to this objection, Applicants have amended the "Brief Description of the Figures" section to recite:

> *Figures 2A-2D show the conjugate obtained was able to enter the eukaryotic cells in culture, wherein the mouse antiGLI IgG-Transportan TP10 conjugate is visualized (FIG. 2A), the mouse FITC-conjugated anti-IgG is visualized (FIG. 2B), the mouse anti-GLI1 (IgG)-Transportan TP10 conjugate is visualized (FIG. 2C), and the mouse FITC-conjugated anti-IgG is visualized (FIG. 2D).*

(c) Figure 3 is objected to for reciting "... the cell penetrating recombinant protein", because it is not clear what is meant.

In response to this objection, Applicants have amended the "Brief Description of the Figures" section to recite:

> *FIG. 3A shows the production and purification of the cell penetrating recombinant GST-GLI3(150-250)-9Arg fusion protein. The figure shows the image of Coomassie brilliant blue-stained SDS-polyacryl-amide gel. Lane 1:*

molecular weight marker. Lane 2: uninduced E. coli cell lysate; Lanes 3 and 4: cell lysate, where the expression of the construct has been induced by IPTG. Lanes 5-8: protein fractions 1-4 eluted from glutathione-agarose.

FIG. 3B shows the internalization of the recombinant fusion protein into human 293 cells. The cells were incubated with recombinant GST-GL13(150-250)-9Arg fusion proteins and fluorescent anti-GST antibodies (upper image) detected their internalization into the cells. The image below depicts the phase-contrast image of the same field.

Reconsideration and withdrawal of the objections are respectfully requested based on the above considerations.

Issues Under 35 U.S.C. § 112, Second Paragraph, Indefiniteness

The Examiner has rejected claim 22 under 35 C.F.R. § 112, second paragraph as being indefinite for the recitation of " ... ScFvpart is derived from the human genome". Applicants respectfully traverse.

In response to this rejection, Applicants have amended claim 22 to recite:

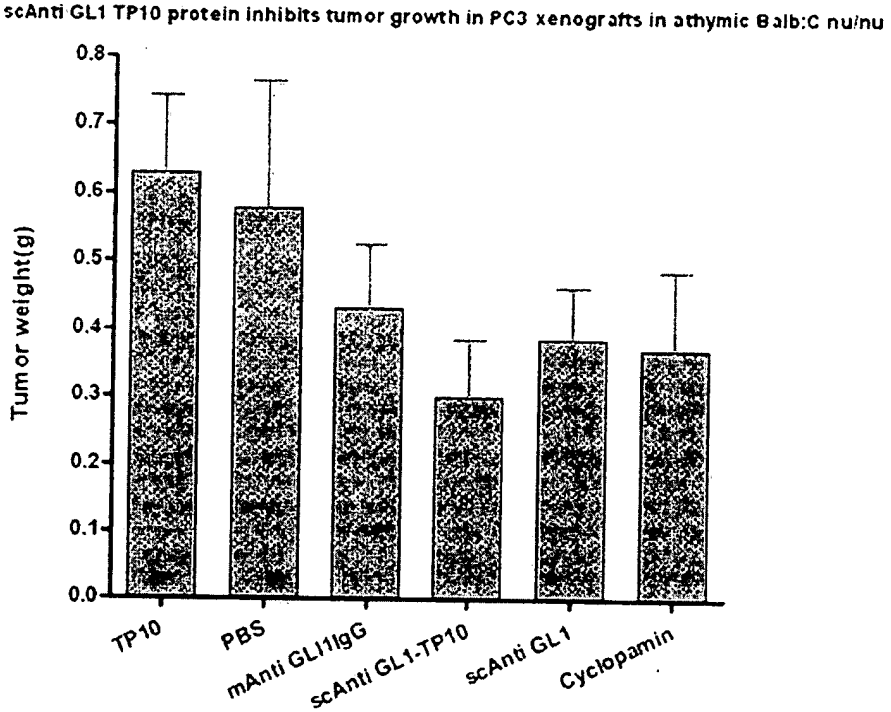
22. Fusion protein according to any one of claims 19 to 21, wherein the scFv-part is ~~derived~~ obtained from the human genome.

Reconsideration and withdrawal of the above rejection is respectfully requested based on this amendment.

Issues Under 35 U.S.C. § 112, First Paragraph, Enablement

The Examiner has rejected claims 23 and 26 under 35 C.F.R. § 112, first paragraph for not reasonably providing enablement for a therapeutical use of the fusion protein in any subject *in vivo* for any disease including cancer much less where the subject is a human. Applicants respectfully traverse.

In responding to this rejection, Applicants argue that it is well known in this art that regulated protein destruction controls many key cellular processes with aberrant regulation increasingly found during carcinogenesis. The present specification teaches that the Gli proteins mediate the transcriptional effects of the Sonic hedgehog pathway, which is implicated in a range of human tumors. It is well known that Gli is rapidly destroyed by the proteasome and that basal cell carcinoma induction correlates with Gli protein accumulation. Applicants have provided in the Information Disclosure Statement (IDS) co-filed herewith, a reference, Muller *et al.* (Drug Discovery Today, Vol 4, pages 285-291, 2007), which teach targets for anti-cancer drugs and correlate these targets with the Gli proteins. This reference provides data that supports the conclusion that control of Gli protein accumulation underlies tumorigenesis and correlates with antitumor therapy. Additionally, Applicants have shown in recent experiments that molecules described in the present application cause reduction of tumor size on mice (see figure below).



As shown in this figure, TP10 itself does not cause any effect as well as PBS (negative controls). Applicants' claimed construct is even more effective than Cyclopamine (positive control, inhibitor of GLI signaling pathway).

Applicants contend that the level of skill in the art is high such that determining the "therapeutically effective amount" and "target cell types" are predictable. Thus, Applicants believe that the claimed product (fusion protein consisting of scFv and transport sequence) is *per se* novel as it is the first time where such fusion protein has been produced and efficacy proven, and making and using the invention as claimed would not cause undue burden on the skilled artisan.

Reconsideration and withdrawal of the above rejection is respectfully requested based on the above-considerations.

Issues Under 35 U.S.C. § 102(b), Anticipation

The following rejections are pending:

(A) Claims 19, 23 and 26 stand rejected under 35 U.S.C. § 102(b) as being anticipated by **Zhao *et al.* (J.Method.Immunol. 254:137-145)**, as evidenced by Pavlinkova *et al* (J. Method. Immunol. 201:77-88); and

(B) Claims 19, 21, 23, and 26 stand rejected under 35 U.S.C. § 102(b) as being anticipated by **Rothbard (WO 98/52614)**.

Applicants respectfully traverse both rejections.

In responding to this rejection, it appears that Zhao *et al.* do not teach a scFv-part of an antibody linked to a cell penetrating transport peptide. Moreover, this reference teaches only *in vitro* applications, not in a medical use or pharmaceutical composition as claimed. It appears that all of the limitations of the claims are not taught. The Examiner states that the method taught by Zhao *et al.* is evidenced by Pavlinkova *et al.* However, the Zhao *et al.* reference is not cited in the article by Pavlinkova *et al.* Pavlinkova *et al.* is drawn to methods of site-specific photo-biotinylation for antibodies of different classes. The teachings of the Pavlinkova *et al.* are incorporated in Zhao *et al.* for its discussion of immunoassays. These biotin complexes are used in antibody based assay systems and not for medical use. In addition, Pavlinkova *et al.* do not teach penetrating transport peptides.

The present claims have been amended to recite a "fusion" protein. A "Fusion protein" is a protein expressed from a contiguous recombinant DNA molecule composed of two or more distinct sequences encoding natural or synthetic polypeptides or parts thereof that are not naturally expressed in contiguity. A defining feature of a fusion protein is that its distinct component sequences share a common backbone formed of covalent peptide bonds between adjacent amino acid residues.

In contrast, Zhao refers to a conjugation construct. "Protein conjugates" are a protein attached to another molecule by chemical or physico-chemical means through covalent linkage usually involving the protein's amino acid side chain moieties. In contrast to recombinant fusion proteins, protein conjugates often consist of a heterogeneous population of reaction products containing variable numbers of conjugated molecules per protein.

Since Zhao refers to conjugation, and not a recombinant fusion protein as claimed, Zhao's method is unpredictable and yields a heterozygous population of cell permeable antibodies, as the process is random. In contrast, Applicants' product has defined quality (homogeneity) as its production involves site-specific insertion of cell membrane permeable sequence.

In regards to the Rothbard *et al.* reference, it appears to be relevant for disclosing polyarginine peptides. Moreover, in the Rothbard *et al.* reference, Example no 4 teach Arg peptides that are conjugated with a fluorescent marker. However, the present claims encompass a recombinant fusion protein comprising at least (a) a scFv-part of an antibody, and (b) a cell penetrating transport peptide. Claim 21 is further distinguished in that this claim recites that the cell penetrating transport peptide is comprised of at least a part of Transportan, Transportan 10 or Arg 9. Rothbard *et al.* do not teach said protein either in conjugation or fusion with Arg peptides.

Example no 12 of the Rothbard *et al.* reference includes Arg peptides in chemical conjugation with ovalbumine. However the present claims are drawn to a recombinant fusion protein comprising at least (a) a scFv-part of an antibody, and (b) a cell penetrating transport peptide.

Legal Standard For Anticipation

The standard for a rejection under 35 U.S.C. § 102(b) is established in MPEP §2131. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. If an independent claim is allowable under 35 U.S.C. § 102, then any claim depending therefrom is also allowable.

Therefore, it is submitted that Zhao *et al.*, as evidenced by Pavlinkova *et al.* or Rothbard *et al*) do not teach each and every limitation of the present claimed invention.

Accordingly, the present invention is *not* anticipated by the Zhao *et al.*, or Rothbard *et al.* reference of record. Any contention of the USPTO to the contrary must be reconsidered at present. Reconsideration and withdrawal of the above rejections are respectfully requested based on the above-considerations.

Issues Under 35 U.S.C. § 103(a) Obviousness

The following rejections are pending:

(A) Claims 19, 20, 23, and 26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over **Zhao *et al.* (J.Method.Immunol. 254:137-145)**, as evidenced by Pavlinkova *et al* (J. Method. Immunol. 201:77-88), in view of **Toftgard (WO 01/12655)**;

(B) Claims 19-21, 23, and 26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over **Zhao *et al*;** as evidenced by Pavlinkova *et al.* in view of **Toftgard (WO 01/12655)** as applied to claims 19, 20, 23 and 26 above, and further in view of **Rothbard (WO 98/98/52614)**, and **Lindgren *et al.* (Trends in Pharm. Sciences 21: 99-103)**;

(C) Claims 19, 21, 23, and 26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over **Rothbard (WO 98/98/52614**, in view of **Lindgren *et al.* (Trends in Pharm. Sciences 21: 99-103)**; and

(D) Claims 19-21, 23, and 26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over **Rothbard (WO 98/98/52614)**, in view of **Lindgren *et al.***

(Trends in Pharm. Sciences 21: 99-103) as applied to claims 19, 21, 23 and 26, and further in view of **Toftgard (WO 01/12655)**.

Applicants respectfully traverse both rejections.

Distinctions Over the Cited Reference

Rothbard (WO 98/98/52614)

Zhao *et al.* (J.Method.Immunol. 254:137-145)

Applicants contend that the arguments described above with respect to distinctions over the Zhao *et al.*, and Rothbard *et al.* references are equally applicable here (and are incorporated herein by reference in their entirety).

Furthermore, in Example no 12 of the Rothbard *et al.* reference, it teach Arg peptides chemical conjugation with ovalbumine, but the patent do not give any experimental data to teach, suggest or provide predictable results for the use of fusion peptides (as now claimed) nor for the intended functionality as disclosed in the specification.

Toftgard (WO 01/12655)

Toftgard teach proteins of a mammalian signaling pathway, namely GLI-1. However the short comings of Zhao *et al.* are not complemented by the disclosure of Toftgard since there are no teachings of the scFv-part of an antibody. Neither Zhao *et al.*, nor Toftgard provide any information on how a scFv peptide behaves when linked to a penetrating transport peptide within a cell. Even if these references are combined, one skilled in the art could not obtain from such a combination any rational reason to arrive at the particular fusion protein claimed.

Lindgren *et al.* (Trends in Pharm. Sciences 21: 99-103)

Lindgren *et al.* teach intracellular delivery of cell penetrating peptides, in particular, the properties of Transportan as a transporter peptide, however, none of the references teach the claimed fusion protein (as now claimed) or the substitutions of known sequences for another to obtain predictable results yielding the claimed fusion proteins.

Applicants again emphasize that it is not obvious without predictable experimental data to make the membrane permeable fusion proteins that will:

1.) enter effectively into cells and

2.) retain their initial biological activity (i.e. specific binding of GLI proteins in our application).

To support this argument, Applicants have provided comparative evidence to establish a substantial degree of unpredictability in this pertinent area with structurally similar fusion protein constructs.

Applicants contend in Exhibit [A] that after testing several sites wherein to link the domains. Applicants have shown that not all the positions are suitable for making the fusion protein. Therefore, Applicants again contend that finding of each working position requires experimental data and is unpredictable.

Applicants believe that it is not obvious, due to the unpredictability of this art, without the exercise of inventive activity for person skilled in the art.

Applicants also argue from Exhibit [A] shows the unexpected results and advantageous properties on the claimed recombinant fusion protein constructs.

Legal Standard for Determining Prima Facie Obviousness

M.P.E.P. § 2143 sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an obviousness analysis. The four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). Second, the Examiner has to provide some rationale for determining obviousness, wherein M.P.E.P. § 2143 set forth some rationales that were set established in the recent decision of *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). Here, the Examiner has

not appropriately resolved the *Graham* factors, including ascertaining the differences between the prior art and the claims that are at issue, and the rationale in combining the cited references is improper.

The rationale should be made explicit, *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), and the Examiner must interpret the reference as a whole and cannot pick and choose only those selective portions of the reference which support the Examiner's position. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention.").

As the M.P.E.P. directs, all claim limitations must be considered in view of the cited prior art in order to establish a *prima facie* case of obviousness. *See* MPEP § 2143.03.

MPEP § 2143.03 recites examples of Basic Requirements of a *Prima Facie* Case of Obviousness and seven exemplary rationales.

Note that the list of rationales provided is not intended to be an all-inclusive list. Other rationales to support a conclusion of obviousness may be relied upon by Office personnel.

However, Applicants fully address these rationales below. According to Applicants analysis below, the Examiner has not met the basic requirements of a *prima facie* case of obviousness. More specifically, Applicants contend that:

(A) Combining prior art elements according to known methods cited do not yield predictable results for the claimed recombinant fusion protein;

(B) Simple substitution of one known domain having biological properties of structurally similar fusion protein constructs, does not yield predictable results in regards to the claimed recombinant fusion protein;

(C) There is no known technique to improve recombinant fusion proteins which one skilled in the art would use to achieve the claimed domains, and in particular, a cell penetrating transport peptide comprised of at least a part of Transportan, Transportan 10 or Arg 9;

(D) Applying known techniques as taught by Zhao *et al.*, and Rothbard *et al.* do not yield predictable results for said recombinant fusion protein constructs as claimed;

(E) The Examiner cannot support the conclusion of "obviousness" on the basis "Obvious to try" – Applicants have presented data showing that there are no predictable methods or models that establish a reasonable expectation of success for said recombinant fusion protein constructs as claimed;

(F) There is no reason or rationale cited by the Examiner that may prompt variations from the disclosure of Zhao *et al.*, and Rothbard *et al.* that would result in the claimed recombinant fusion proteins;

(G) There is no proper teaching, suggestion, motivation, and/or reasonable expectation of success that would yield predictable results in the prior art as cited by the Examiner that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed recombinant fusion proteins.

Accordingly, the present invention is *not* rendered obvious in view of the teachings and disclosures of the cited modification of the cited prior art. Any contentions of the USPTO to the contrary must be reconsidered at present. Reconsideration and withdrawal of the above rejections are respectfully requested based on the above-considerations.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Eggerton A. Campbell Reg. No. 51,307 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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Attachments: 1) Exhibit A
2) Sequence Listing
3) Supplemental Application Data sheet
4) Information Disclosure Statement